

The James Madison Project
1275 K Street, N.W.
Suite 770
Washington, D.C. 20005

(202) 785-3801
(202) 371-6643 fax

E-Mail: JaMadPro@aol.com
<http://www.jamesmadisonproject.org>

February 11, 2000

VIA CERTIFIED MAIL

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Re: Anthrax Vaccine Adsorbed Product Insert

To Whom It May Concern:

The undersigned submits this petition pursuant to 21 C.F.R. §§ 10.20, 10.30, 314.80, 314.81, 314.93, 314.540 and any and all other applicable regulations or statutes to request the Commissioner of Food and Drugs to amend the product insert and/or label for Anthrax Vaccine Adsorbed, U.S. license number 1260 (rev. 3/99), that is currently manufactured by the BioPort Corporation.

A. Action requested

The current product insert, a full copy of which is enclosed as Exhibit "1", states the following:

Systemic Reactions: Systemic reactions which occur in fewer than 0.2 per cent of recipients have been characterized by malaise and lassitude. Chills and fever have been reported in only a few cases. In such cases, immunization should be discontinued.

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The revised product insert should be amended to read:

Systemic Reactions: Systemic reactions occur in 5-35 per cent of recipients, and have included reports of malaise, lassitude, chills, rashes, headaches and low-grade fever. In such cases, immunization should be discontinued. Women report these systems more often than men.

B. Statement of grounds

1. Factual Summary

BioPort's facility has been licensed to manufacture the anthrax vaccine since 1970, after receiving approval from the Division of Biologics Standards, National Institutes of Health.¹ Prior to Operation Desert Storm, the primary market for the anthrax vaccine was laboratory, veterinary, and industrial workers at risk of exposure to naturally occurring anthrax. Before 1990, only about 30,000 individuals had received the vaccine. During Desert Storm, however, approximately 150,000 service members received the anthrax vaccine. Unfortunately accurate medical records do not exist to confirm the number of recipients, nor apparently were any studies or monitoring undertaken by the Department of Defense (DoD) to measure the adverse reaction rate.

With the end of Desert Storm, the urgent need for the anthrax vaccine was no longer valid. By 1995, however, the DoD was determined to implement a force-wide anthrax program. On December 15, 1997, Secretary of Defense William S. Cohen announced the implementation of a military-wide anthrax immunization plan. Vaccinations began with select service members in March 1998. On May 18, 1998, Secretary of Defense Cohen approved implementation of the program for the total force.

The Secretary of Defense named the Secretary of the Army as the Executive Agent for the Anthrax Vaccine Immunization Program (AVIP). The AVIP Agency was created to

¹The Michigan Department of Public Health was granted the original license to produce the anthrax vaccine in 1970. In 1995, the facility changed its name to the Michigan Biologic Products Institute. In 1998, the facility was sold, and its name was changed to BioPort.

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serve under the direction of the Army Surgeon General and the Assistant Surgeon General for Force Projection. The Agency is the Department's central source for AVIP information and education products and manages the AVIP internet Web site and toll-free information line; they daily support requests for information from commanders in the field, service members, DoD civilians, family members, the media, Congress, and the American public.

2. Systemic Adverse Reaction Rates:

The systemic reaction rate² listed on the product insert is inaccurate and outdated. It was derived from the original licensure study published in 1962.³ Since that time, there have been numerous studies conducted by the United States Government that prove the systemic adverse reaction rate is significantly greater - up to 70 times - than listed on the insert.

The evidence supporting a change in the product insert is based directly on internal documents received from the DoD, many of which were unpublished and withheld from the public until released as a result of litigation under the Freedom of Information Act, Veterans for Integrity in Government v. Department of the Army et al., Civil Action No. 98-1649 (D.D.C. June 29, 1998)(RWR), and congressional testimony.

The initial documents revealed through litigation exposed systemic adverse reaction rates that were up to seven times greater than indicated on the product insert (copies of the supporting documentation are enclosed as Exhibits "2" through "4"):

²The DoD AVIP website (<http://www.anthrax.osd.mil/>) defines "systemic" as "relating to or affecting the body as a whole, rather than individual parts and organs." (The Bantam Medical Dictionary, 1994, Market House Books Ltd). Thus, "a systemic reaction, in reference to an injectable medication, is a reaction that occurs away from the site of injection. A 'systemic reaction' is not synonymous with a 'severe reaction'. Since fever, chills, malaise, lassitude, etc., effect more than just the site of injection they are properly categorized as systemic reactions."

³PS Brachman et al., Field Evaluation of Human Anthrax Vaccine, 52 Amer.J.Pub.Health 632-45 (1962).

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Systemic Reaction Rates

First Shot (1.33%)
 First Shot (0.9%)
 Second Shot (0.6%)
 Second Shot (0.4%)
 Third Shot (0.2%)
 Boosts (0.5%)
 MDPH Vaccine (0.7-1.3%)

Source of Information

USAMRIID, Fall 1990-Spring 1991
 USAMRIID, 1977-1994
 USAMRIID, Fall 1990-Spring 1991
 USAMRIID, 1977-1994
 USAMRIID, 1977-1994
 USAMRIID, 1977-1994
 USAMRIID, 1998

The DoD, until late 1999, sought to downplay the significance of the number of systemic reactions experienced during their studies. Systemic reactions of 0.2% or more were being labeled as "very rare". Fever and chills, both classic examples of systemic reactions, became re-categorized as a "severe local reaction". In its original 1998, brochure "What Every Soldier, Sailor, Airman and Marine Should Know About The Anthrax Vaccine", which was made available to servicemen in each branch, the DoD noted that less than 1% of those who receive the anthrax vaccine should experience fever. Additionally, for more than one year into the program, the DoD routinely stressed misleading figures concerning the adverse reaction rates experienced by recipients of the anthrax vaccine in order to disguise the true figures. For example, the figure .0002 percent was often asserted as the actual side effect reaction rate, as cited by Navy Rear Admiral Michael Cowan, medical readiness director on the Joint Staff, in a November 20, 1998, article issued by the American Forces Press Service, a copy of which is enclosed as Exhibit "5". This number, however, was knowingly scientifically irrelevant as it was derived from dividing the number of *self-reported* adverse reactions by the number of doses of the vaccine that had been administered. As the discussion on adverse reaction reporting addresses below, there is little value to such statistics given that the actual number of those who *suffered* adverse reactions is unknown. Based on the surfacing of internal government documents to the contrary, even the DoD - as indicated below - has admitted these figures no longer have a valid factual basis.

The evidence on the true systemic adverse reaction rate was revealed during many of the congressional hearings held on the anthrax vaccination program by the House of Representatives. On April 29, 1999, Kwai Chan, Director of Special Studies and Evaluations National Security and International Affairs Division, General Accounting Office (GAO), testified before the House Government Reform Committee's Subcommittee on National Security, Veterans Affairs and International Relations. A copy

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of Chan's testimony is enclosed as Exhibit "6". The GAO provided evidence regarding four safety studies conducted on the licensed vaccine. The Center for Disease Control collected data on the Investigational New Drug (IND) study, and the DoD collected data for both the Pittman study and the Tripler Army Medical Center (TAMC) Anthrax Survey. The GAO revealed that the number of adverse reactions depends, in part, upon whether the mechanism for monitoring reactions is active or passive (Active monitoring means that the vaccine recipients are contacted to ascertain any adverse reactions after vaccine administration; passive monitoring means that the onus is on the vaccine recipients to report any adverse reactions after vaccine administration).

The systemic adverse reaction results in those studies are reproduced below:

Reactions to Licensed Anthrax Vaccine Reported in Various Studies

Study	Reporting	# Vaccinated(or doses)	Systemic reactions(%)	
			Mild	Moderate/Severe
IND	Active/Passive	3,984 ^a	None ^b	.05 ^b
Study	Reporting	# Vaccinated(or doses)	Systemic reactions(%)	
			Mild	Moderate/Severe
Pittman (1997)	Active	508	29 ^c	14
TAMC (1998)	Active	536	43 ^d	5

^aThis number represents the number of study participants who received the first dose of the licensed vaccine.

^bThese figures represent the percentage of people who experienced this type of reaction during the study, even if they had previously been inoculated with the Merck vaccine.

^cThis figure also includes persons who had reactions of "unknown" severity.

^dThis figure represents the frequency of the most common side effect, myalgia.

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The GAO presented additional findings concerning systemic adverse reactions to the Congress on July 21, 1999, a copy of which is attached as Exhibit "7", based on information reported through the Vaccine Adverse Reporting System (VAERS)⁸ and three DoD efforts to actively collect data on adverse reactions after servicemembers received the anthrax vaccine. Additionally, it was revealed that women reported twice the rate of adverse reactions than men for systemic reactions.

The statistics and findings contained in the July 21, 1999, GAO report are self-explanatory. Most importantly, the figures are not contested - but rather supported - by the DoD. A January 6, 2000, report on the *Safety Review of Anthrax Vaccine*, that was compiled by the AVIP Agency and posted on its Web site, adopts the GAO's findings. A copy of the AVIP report is enclosed as Exhibit "8". The AVIP report details information on twelve studies that have been completed or are still on-going regarding the anthrax vaccine. Some of the more relevant statistics are provided below:

⁸Of course, VAERS has several disadvantages and the statistical information cannot be used as a true indicator. "Studies show that adverse events are often underreported in a passive surveillance system. A former FDA commissioner acknowledged the underreporting of adverse events in passive surveillance systems and cited one study showing that 'only about 1 percent of serious events' attributable to drug reactions are reported to FDA. Outcomes with delayed onset after vaccination or outcomes not generally recognized to be associated with vaccination are often underreported. According to the National Vaccine Information Center, there is no mechanism within VAERS for a 1-, 3-, or 10-year follow-up to evaluate vaccine reactions that have a long latency period. According to CDC, the limitations of VAERS data suggest it is not a valid source for assessing the rate of adverse events." GAO Report, Medical Readiness: Issues Concerning the Anthrax Vaccine (GAO/T-NSIAD-99-226, July 21, 1999)(citations omitted)(citations omitted).

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Study	Date	Systemic Adverse Reaction Rate
Fort Bragg Booster	1992-93	One or more systemic reactions occurred in 44% of recipients during the first 30 days after vaccination, most commonly muscle aches (30%), malaise (16%), headache (16%), rash (16%), or joint aches (12%). ⁹
USAMRIID Reduced-Dose/ Route-Change	1998	After the first dose, the side effects noted were headache (14%), malaise (9%), loss of appetite (3%), nausea or vomiting (3%), muscle ache (3%), itching (3%) and low grade fever (3%).
U.S. Forces Korea Records	1998-99	Itching was reported by 22% to 40% of women and 7% to 9% of men. Fever was reported by 3% to 5% of women and 1% to 2% of men. Chills were reported by 4% to 6% of women and 2% of men. Malaise was reported by 15% to 16% of women and 6% to 7% of men.

The true figure of 5% to 35% for systemic reactions have been officially confirmed by the DoD on numerous occasions, including by the Surgeon General of the United States Department of the Army, the leading medical official implementing the AVIP. In a letter dated December 10, 1999, to the undersigned, a copy of which is enclosed as Exhibit "9", Lieutenant General Ronald R. Blanck admits that "[s]ystemic events occur in *five to 35 percent* of anthrax-vaccine recipients." (emphasis added). Additionally, the latest Defense Department quadfold (dated November 1, 1999) - "*What Everyone Needs To Know About The Anthrax Vaccine*" - that is distributed to service members and their families, states:

⁹It was noted that those individuals vaccinated were engaged in field exercise at the time of inoculation.

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Beyond the injection site, from 5% to 35% will notice muscle aches, joint aches, headaches, malaise, rashes, chills, low-grade fever, nausea, or related symptoms.

These symptoms refer, of course, to systemic adverse reactions. A copy of this quadfold is enclosed as Exhibit "10", and can also be found at the AVIP Web site <http://www.anthrax.osd.mil/>. Furthermore, also on the AVIP Web site is a power point slide, enclosed as Exhibit "11", that acknowledges the same range of systemic reactions. The same slide indicates that "women report these systems more often than men."

These issues are by no means of minor significance. The current DoD anthrax program, once fully implemented, will require approximately 2.5 million people to receive the vaccine. To date, more than 400,000 service members have received one or more shots of the vaccination series. It is imperative - both as a matter of law and morality - that accurate information is provided to vaccine recipients so that adverse reactions can be properly identified and treated.

In his opening statement before the July 21, 1999, oversight hearing on the AVIP, Congressman Shays said "[t]he practice of medicine, not public relations, should be driving the adverse event reporting process. Whether the adverse reaction rate is two tenths of one percent or 21 percent, DoD has an obligation to protect those in the force made ill by this force protection program. If women suffer adverse health effects at twice the rate of men, DoD has an obligation to acknowledge and ameliorate those effects." For the most part, after more than one year of public discussion on these issues, the DoD has accepted its responsibility. The FDA also has an obligation to protect those who receive the anthrax vaccine. Given that the present product insert label for the anthrax vaccine does not reflect accurate information concerning systemic adverse reactions, it is the FDA's responsibility to ensure that it does.

C. Environmental impact

There is no environmental impact imposed by the relief requested in this petition.

D. Economic impact

Not applicable at this time.

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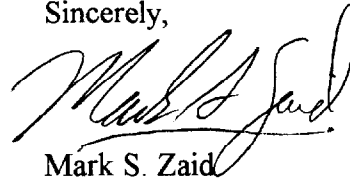
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E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Should you require additional information, would like to discuss this petition, or desire a presentation of the evidence, please do not hesitate to contact me.

Sincerely,



Mark S. Zaid
Executive Director

Enclosures:

- (1) Anthrax Vaccine Adsorbed, Product Insert;
- (2) Anthrax Vaccine Reaction Rates, USAMRIID, Fall 1990-Spring 1991;
- (3) Anthrax Vaccination Reactions, Primary Series, Special Immunizations Clinic, USAMRIID, Ft. Detrick, MD, 1977-94, June 1994 (Unpublished Data);
- (4) USAMRIID Briefing Slide, 1998;
- (5) "Anthrax vaccine called force protection", American Forces Press Service, Nov. 20, 1998;
- (6) Congressional testimony of Kwai Chan, Director of Special Studies and Evaluations National Security and International Affairs Division, General Accounting Office, April 29, 1999 - *Medical Readiness: Safety and Efficacy of the Anthrax Vaccine* (GAO/T-NSIAD-99-148, Apr. 29, 1999);
- (7) Congressional testimony of Kwai Chan, Director of Special Studies and Evaluations National Security and International Affairs Division, General Accounting Office, July 21, 1999 - *Medical Readiness: Issues Concerning the Anthrax Vaccine* (GAO/T-NSIAD-99-226, July 21, 1999);
- (8) *Safety Review of Anthrax Vaccine*, January 6, 2000, published on the AVIP Web site at <http://www.anthrax.osd.mil/>;

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(9) Letter dated December 10, 1999, from Lieutenant General Ronald R. Blanck to Mark S. Zaid;

(10) Defense Department Quadfold, *"What Everyone Needs To Know About The Anthrax Vaccine"* November 1, 1999;

(11) AVIP Power Point Slide "Systemic Events", December 7, 1999, located at <http://www.anthrax.osd.mil//SCANNED/ARTICLES/briefings/HCPBrief/sld036.htm>.

cc: Dr. Jane E. Henney

Commissioner, FDA

Dr. Kathryn C. Zoon

Director, Center for Biologics Evaluation and Research, FDA

Dr. Robert Myers

Chief Operating Officer, BioPort

LTC Gaston Randolph

Director, AVIP Office

Dr. John Sever

Chairman, Anthrax Vaccine Expert Committee

Congressman Walter Jones

Congressman Benjamin Gilman

Congressman Christopher Shays

Congressman Dan Burton

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